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IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT,
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ning of each regular issue of the PCT Gazette.*



WO 01/44239 A3

(54) Title: BIPHENYL SULFONAMIDES AS DUAL ANGIOTENSIN ENDOTHELIN RECEPTOR ANTAGONISTS

(57) Abstract: Novel biphenyl sulfonamide compounds which are combined angiotensin and endothelin receptor antagonists are claimed along with methods of using such compounds in the treatment of conditions such as hypertension and other diseases, as well as pharmaceutical compositions containing such compounds.

INTERNATIONAL SEARCH REPORT

International Application No

PC US 00/33730

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07D413/12 C07D413/14 C07D403/14 C07D487/04 C07D261/16
 C07D401/12 C07D417/12 A61K31/42 A61P9/12

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, PAJ, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 5 612 359 A (MURUGESAN) 18 March 1997 (1997-03-18) column 4, line 58 -column 6, line 2; claims; example 15 ---	1-46
X	US 5 846 990 A (MURUGESAN) 8 December 1998 (1998-12-08) claims; examples ---	26
Y	US 5 780 473 A (MURUGESAN ET. AL.) 14 July 1998 (1998-07-14) column 6, line 33 -column 7, line 45; claims; examples ---	1-46
Y	US 5 514 696 A (MURUGESAN ET. AL.) 7 May 1996 (1996-05-07) column 5, line 13 -column 6, line 2; claims; examples ---	1-46
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☒ Further documents are listed in the continuation of box C.☒ Patent family members are listed in annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

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"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

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"&" document member of the same patent family

Date of the actual completion of the international search

15 May 2001

Date of mailing of the international search report

29.05.01

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INTERNATIONAL SEARCH REPORT

International Application No

PC JS 00/33730

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	GB 2 264 710 A (MERCK & CO) 8 September 1993 (1993-09-08) claims; examples ---	1-46
X	WO 98 33780 A (BRISTOL MYERS SQUIBB) 6 August 1998 (1998-08-06) claims; examples ---	1,26,39
X	WO 98 04260 A (BRISTOL MYERS SQUIBB) 5 February 1998 (1998-02-05) claims; examples ---	26
Y	US 5 554 625 A (RIVERO ET. AL.) 10 September 1996 (1996-09-10) claims; examples ---	1
Y	US 5 399 578 A (BÜHLMAYER ET. AL.) 21 March 1998 (1998-03-21) claims; examples ---	1,39
Y	US 5 260 328 A (MARKWALDER ET. AL.) 9 November 1993 (1993-11-09) column 2, line 1 - line 38; claims; examples ---	1,39
Y	US 5 760 038 A (MURUGESAN ET. AL.) 2 June 1998 (1998-06-02) claims; examples -----	1

INTERNATIONAL SEARCH REPORT

international application No.
PCT/US 00/33730

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
Although claim 23 is directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. ☒ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☒ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. Claims: 1(part),2-25,27-31,32(part),33-37,39-46

Compounds of formula I in which R1 is A, B, E, G - N

2. Claims: 1(part),32(part),38

Compounds of formula I in which R1 is D

3. Claim : 1(part)

Compounds of formula I in which R1 is F

4. Claim : 1(part)

Compounds of formula I in which R1 is O

5. Claim : 26

Compounds of formula LXX.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

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International Application No

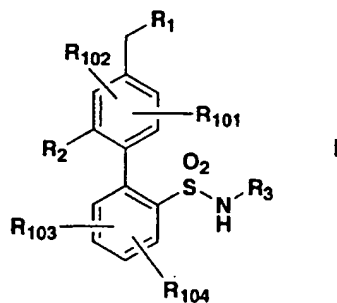
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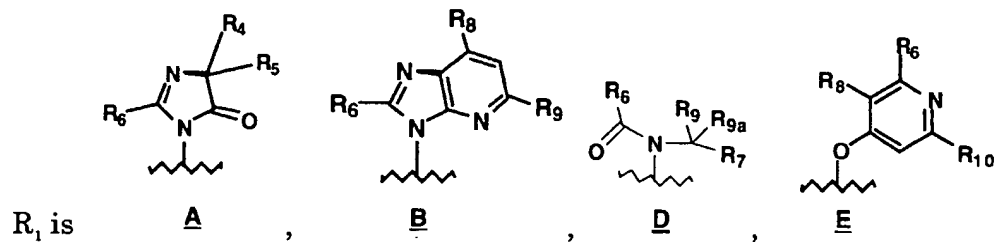
What is claimed is:

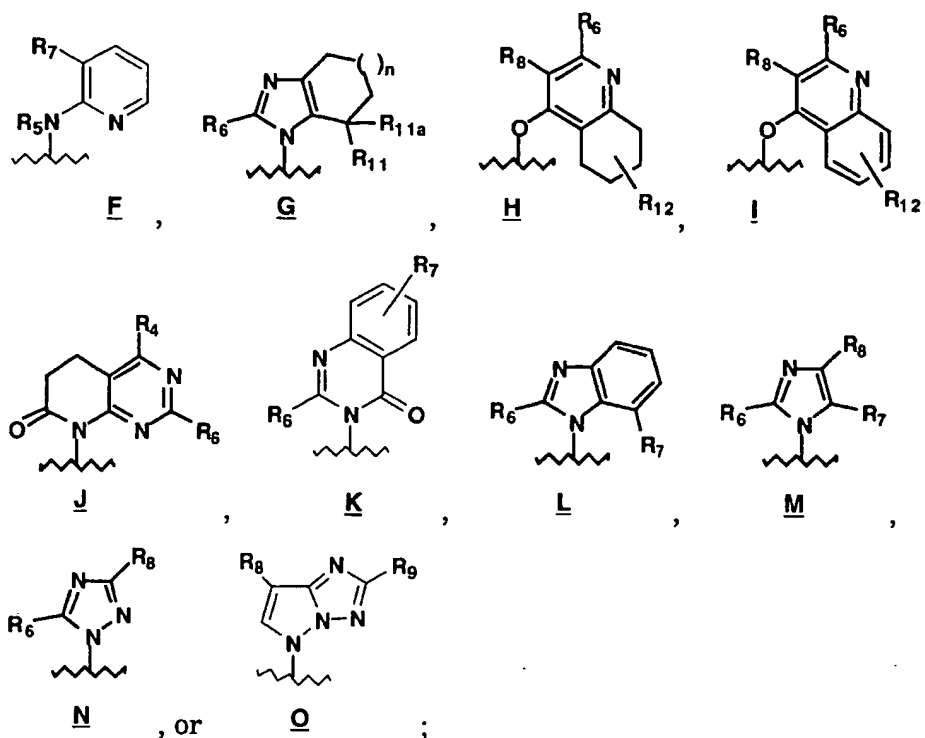
1. A compound of the following formula I, or an enantiomer, diastereomer, salt or metabolite thereof:

5



wherein:





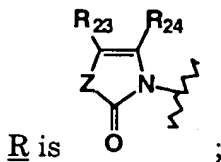
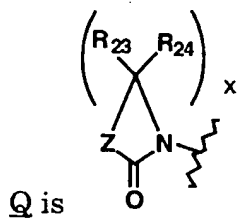
R_2 is hydrogen, halogen, -CHO, alkyl, haloalkyl, (cycloalkyl)alkyl, alkenyl,
 5 alkynyl, alkoxyalkyl, haloalkoxyalkyl, alkoxy, aryloxy alkoxyalkoxy,
 cyano, hydroxy, hydroxyalkyl, nitro, $-\text{CH}(\text{OR}_{13})(\text{OR}_{14})$, $-(\text{CH}_2)_w\text{Y}$;
 with the proviso that when R_1 is **B**, R_2 is not hydrogen, halogen,
 alkyl, haloalkyl, alkoxy, hydroxyalkyl, nitro, $-(\text{CH}_2)_w\text{NR}_{19}\text{R}_{20}$ or
 $-\text{NHSO}_2\text{R}_{22}$;

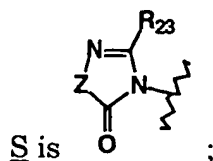
10 R_3 is heteroaryl;

R_4 and R_5 are each independently alkyl, hydroxyalkyl, cycloalkyl, hydroxy
 substituted cycloalkyl, alkoxyalkyl, or hydroxy substituted
 alkoxyalkyl, or R_4 and R_5 together form a cyclobutyl, cyclopentyl,
 cyclohexyl, tetrahydrofuranyl or tetrahydropyranyl ring which may
 15 be optionally substituted with one or more hydroxy groups;

R_6 is alkyl, hydroxyalkyl, haloalkyl, hydroxy substituted haloalkyl,
 cycloalkyl, hydroxy substituted cycloalkyl, (cycloalkyl)alkyl,
 hydroxy substituted (cycloalkyl)(alkyl), aralkyl, alkoxy, hydroxy
 substituted alkoxy, alkoxyalkyl, hydroxy substituted alkoxyalkyl, or
 20 $-\text{NR}_{16}\text{R}_{17}$;

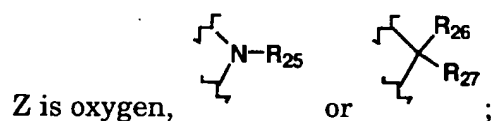
- R_7 is $-(CH_2)_w-CO_2R_{15}$, $-(CH_2)_w-(C=O)NR_{16}R_{17}$, $-(CH_2)_w-NR_{15}(C=O)NR_{16}R_{17}$, $-(CH_2)_w-CH_2OH$, $-(CH_2)_w-(C=O)R_{15}$, tetrazolyl, oxadiazolyl or triazolyl wherein said tetrazolyl, oxadiazolyl or triazolyl may optionally be substituted with hydrogen, alkyl, hydroxy or halogen;
- 5 R_8 , R_9 , R_{9a} , R_{10} and R_{12} are each independently hydrogen, halogen, alkyl, hydroxyalkyl, cycloalkyl, (cycloalkyl)alkyl, aryl, heteroaryl, arylalkyl, alkylthioalkyl, alkoxy or alkoxyalkyl, or R_9 and R_{9a} together with the carbon atom to which they are bonded form a cycloalkyl ring;
- 10 R_{11} and R_{11a} are each independently hydrogen, alkoxy, or together form a carbonyl;
- R_{13} and R_{14} are alkyl or together form a five to six-membered ring;
- R_{15} , R_{16} and R_{17} are independently hydrogen, alkyl, hydroxyalkyl, cycloalkyl, (cycloalkyl)alkyl, alkoxyalkyl, aralkyl, heterocycloalkyl,
- 15 aryl, heteroaryl or $-(CH_2)_wQ$, or R_{16} and R_{17} may together form a four to six-membered heterocyclic ring;
- n is 1 or 2;
- w is 0, 1, or 2;
- Y is heteroaryl, $-COOH$, $-COOR_{18}$, $-CONR_{19}R_{20}$, $-NR_{19}R_{20}$, $-NR_{19}-OR_{20}$,
- 20 $-NR_{21}(C=O)R_{22}$, $-NR_{21}(C=O)NR_{19}R_{20}$, $-N(R_{19})-(alk)-NR_{21}(C=O)R_{22}$, $-NR_{21}(C=O)OR_{18}$, $-NR_{21}SO_2R_{22}$, $-SO_2R_{22}$, Q , R or S ;





R_{18} , R_{19} , R_{20} , R_{21} and R_{22} are each independently hydrogen, alkyl, haloalkyl, alkoxyalkyl, cycloalkyl, alkenyl, alkynyl, aryl, aralkyl, heteroaryl, or R_{19} and R_{20} may together form a four to seven-membered heterocyclic ring;

R_{23} and R_{24} are each independently hydrogen, alkyl or cycloalkyl, or may together form a three to seven membered cycloalkyl ring;

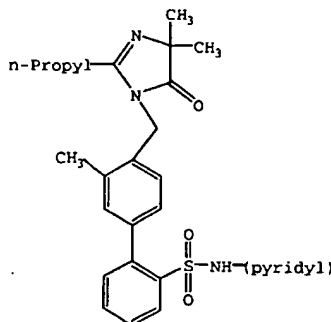


x is 2, 3 or 4;

R_{25} , R_{26} and R_{27} are each independently hydrogen, alkyl or cycloalkyl, or R_{26} and R_{27} may together form a three to seven-membered cycloalkyl ring;

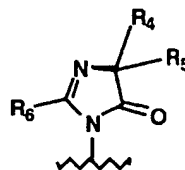
R_{101} , R_{102} , R_{103} , and R_{104} are each independently hydrogen, halogen, -CHO, alkyl, haloalkyl, (cycloalkyl)alkyl, alkenyl, alkynyl, alkoxyalkyl, haloalkoxyalkyl, alkoxy, alkoxyalkoxy, cyano, hydroxy, hydroxyalkyl, nitro, -CH(OR₁₃)(OR₁₄), or -(CH₂)_wY; wherein said rings; aryl alone or as part of another group; or heteroaryl alone or as part of another group may each optionally be substituted by one or more hydrogen, halogen, cyano, alkyl, hydroxyalkyl, alkoxy, nitro or trifluoromethyl groups;

provided that when R_1 is A said compound is other than



2. A compound of claim 1, wherein R_3 is isoxazol-5-yl or isoxazol-3-yl independently substituted with two substituents independently selected from alkyl or halogen.

5



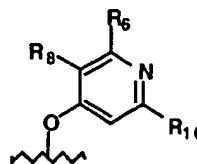
3. A compound of claim 2, wherein R_1 is

A

4. A compound of claim 3, wherein R_2 is alkyl, haloalkyl, alkoxyalkyl or haloalkoxyalkyl and R_{101} , R_{102} , R_{103} , R_{104} are each
10 independently hydrogen, halogen, or alkyl.

5. A compound of claim 3, wherein R_2 is $-CH_2Y$.

6. A compound of claim 5, wherein Y is Q.



15

7. A compound of claim 2, wherein R_1 is

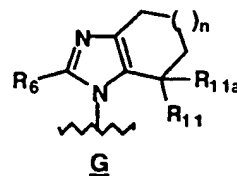
E

8. A compound of claim 7, wherein R_2 is alkyl, haloalkyl, alkoxyalkyl or haloalkoxyalkyl and R_{101} , R_{102} , R_{103} , R_{104} are each
independently hydrogen, halogen, or alkyl.

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9. A compound of claim 7, wherein R_2 is $-CH_2Y$.

10. A compound of claim 9, wherein Y is Q.



11. A compound of claim 2, wherein R_1 is G.
12. A compound of claim 11, wherein R_2 is alkyl, haloalkyl, alkoxyalkyl or haloalkoxyalkyl and R_{101} , R_{102} , R_{103} , R_{104} are each independently hydrogen, halogen, or alkyl.
13. A compound of claim 11, wherein R_2 is $-\text{CH}_2\text{Y}$.
14. A compound of claim 13, wherein Y is Q.
15. A compound of claim 1, wherein R_2 is alkoxyalkyl alkyl, haloalkyl or haloalkoxyalkyl
16. A compound of claim 15, wherein R_3 is isoxazol-5-yl or isoxazol-3-yl independently substituted with two substituents selected from alkyl or halogen.
17. A compound of claim 1, wherein R_2 is $-\text{CH}_2\text{Y}$.
18. A compound of claim 17, wherein R_3 is isoxazol-5-yl or isoxazol-3-yl independently substituted with two substituents selected from alkyl or halogen.
19. A compound of claim 17, wherein Y is Q.
20. A compound of claim 19, wherein R_3 is isoxazol-5-yl or isoxazol-3-yl independently substituted with two substituents selected from alkyl or halogen.

21. A compound of claim 1, wherein said compound is selected from
 N,4-Diethyl-1-[[2'-[[4,5-dimethyl-3-isoxazolyl)amino]sulfonyl-2-
 methyl][1,1'-biphenyl]-4-yl)methyl]-2-propyl-1H-imidazole-5-carboxamide;
 5 1-[[2'-[[4,5-dimethyl-3-isoxazolyl)amino]sulfonyl-2-methyl][1,1'-biphenyl]-4-
 yl)methyl]-4-ethyl-N-(1-methylethyl)-2-propyl-1H-imidazole-5-carboxamide;
 N-(4,5-Dimethyl-3-isoxazolyl)-2'-ethoxymethyl-4'-[[6-ethyl-3-methoxy-2-
 methyl-4-pyridinyl)oxy)methyl] [1,1'-biphenyl]-2-sulfonamide;
 4'-[(5-Acetyl-4-ethyl-2-propylimidazol-1-yl)methyl]-N-(4,5-dimethyl-
 10 3-isoxazolyl)-2'-methyl[1,1'-biphenyl]-2-sulfonamide;
 N-(4,5-Dimethyl-3-isoxazolyl)-4'-[[6-ethyl-3-methoxy-2-methyl-4-
 pyridinyl)oxy)methyl]-2'-propyl [1,1'-biphenyl]-2-sulfonamide;
 and salts, enantiomers, diastereomers and metabolites thereof.
22. A compound of claim 1, wherein said compound is selected from
 N,4-Diethyl-1-[[2'-[[3,4-dimethyl-5-isoxazolyl)amino]sulfonyl-2-
 methyl][1,1'-biphenyl]-4-yl)methyl]-2-propyl-1H-imidazole-5-carboxamide;
 1-[[2'-[[3,4-dimethyl-5-isoxazolyl)amino]sulfonyl-2-methyl][1,1'-
 biphenyl]-4-yl)methyl]-4-ethyl-N-(1-methylethyl)-2-propyl-1H-imidazole-5-
 20 carboxamide;
 N-(3,4-Dimethyl-5-isoxazolyl)-2'-ethoxymethyl-4'-[[6-ethyl-3-
 methoxy-2-methyl-4-pyridinyl)oxy)methyl] [1,1'-biphenyl]-2-sulfonamide;
 4'-[(5-Acetyl-4-ethyl-2-propylimidazol-1-yl)methyl]-N-(3,4-dimethyl-
 5-isoxazolyl)-2'-methyl[1,1'-biphenyl]-2-sulfonamide;
 25 N-(3,4-Dimethyl-5-isoxazolyl)-4'-[[6-ethyl-3-methoxy-2-methyl-4-
 pyridinyl)oxy)methyl]-2'-propyl [1,1'-biphenyl]-2-sulfonamide;
 (S)-2-[N-[2'-[[N-(5-Methyl-3-isoxazolyl)amino]sulfonyl][1,1'-
 biphenyl]-4-yl)methyl]-N-(1-oxopentyl)amino]-3,N-dimethylbutanamide;
 (S)-2-[N-[2'-[[N-(4-Bromo-5-methyl-3-isoxazolyl)amino]sulfonyl][1,1'-
 30 biphenyl]-4-yl)methyl]-N-(1-oxopentyl)amino]-3,N-dimethylbutanamide;
 4'-[(2-Ethylquinolin-4-yl)oxymethyl]-N-(5-methylisoxazol-3-yl)

- [1,1'-biphenyl]-2-sulfonamide;
4'-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-N-(4-bromo-5-methyl-3-isoxazolyl)-2'-[(3,3-dimethyl-2-oxo-1-pyrrolidinyl)methyl][1,1'-biphenyl]-2-sulfonamide;
- 5 N-[[4-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-2'-[[4,5-dimethyl-3-isoxazolyl)amino]sulfonyl][1,1'-biphenyl]-2-yl)methyl]-N-methyl-2-pyrazinecarboxamide;
N-[[2'-[(4,5-Dimethyl-3-isoxazolyl)amino]sulfonyl][1,1'-biphenyl]-4-yl)methyl]-N-(1-oxopentyl)-L-valine;
- 10 4'-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-2'-cyano-N-(4,5-dimethyl-3-isoxazolyl)[1,1'-biphenyl]-2-sulfonamide;
(S)-N-[[2'-[(4,5-Dimethyl-3-isoxazolyl)amino]sulfonyl][1,1'-biphenyl]-4-yl)methyl]-N-(1-piperidinyl)carbonylpropylpentanamide;
and salts, enantiomers, diastereomers and metabolites thereof.
- 15
23. A method for the treatment of an endothelin-dependent or angiotensin II-dependent disorder (such as hypertension, pulmonary hypertension, primary pulmonary hypertension, low renin hypertension, male erectile dysfunction, male or female sexual dysfunction, heart failure, atherosclerosis, restenosis, endotoxemia, inhibition of cell growth, cancer, migraine, asthma, ischemia, subarachnoid hemorrhage, benign prostatic hypertrophy, renal glomerular or mesangial cell disorders, acute or chronic renal failure, chronic obstructive pulmonary disease, pain associated with prostate cancer, organ damage associated with the cell
- 20 poliferative effects of endothelin, general morbidity and mortality associated with endothelin-dependent or angiotensin II-depedendent disorders, diabetic nephropathy, and dementia), comprising the step of administering to a subject in need thereof an amount effective therefor of at least one compound of claim 1.

24. A pharmaceutical composition for the treatment of an endothelin-dependent or angiotensin II-dependent disorder, comprising a pharmaceutically acceptable vehicle or diluent and at least one compound of claim 1 in an amount effective therefor.

5

25. A compound of claim 1, wherein said compound is selected from the group consisting of:

- N-(4,5-Dimethyl-3-isoxazolyl)-4'-[[6-ethyl-3-methoxy-2-methyl-4-pyridinyl]oxy]methyl]-2'-ethyl [1,1'-biphenyl]-2-sulfonamide;
- 10 N-(3,4-Dimethyl-5-isoxazolyl)-4'-[[6-ethyl-3-methoxy-2-methyl-4-pyridinyl]oxy]methyl]-2'-ethyl [1,1'-biphenyl]-2-sulfonamide;
- N-(4,5-Dimethyl-3-isoxazolyl)-4'-[[3-methoxy-2-methyl-6-propyl-4-pyridinyl]oxy]methyl]-2'-ethyl [1,1'-biphenyl]-2-sulfonamide;
- 15 N-(3,4-Dimethyl-5-isoxazolyl)-4'-[[3-methoxy-2-methyl-6-propyl-4-pyridinyl]oxy]methyl]-2'-ethyl [1,1'-biphenyl]-2-sulfonamide;
- N-(4,5-Dimethyl-3-isoxazolyl)-4'-[[3-methoxy-2-methyl-6-propyl-4-pyridinyl]oxy]methyl]-2'-(ethoxymethyl) [1,1'-biphenyl]-2-sulfonamide;
- N-(3,4-Dimethyl-5-isoxazolyl)-4'-[[3-methoxy-2-methyl-6-propyl-4-pyridinyl]oxy]methyl]-2'-(ethoxymethyl) [1,1'-biphenyl]-2-sulfonamide;
- 20 N-(4,5-Dimethyl-3-isoxazolyl)-4'-[[3-methoxy-2-methyl-6-propyl-4-pyridinyl]oxy]methyl]-2'-propyl [1,1'-biphenyl]-2-sulfonamide;
- N-(3,4-Dimethyl-5-isoxazolyl)-4'-[[3-methoxy-2-methyl-6-propyl-4-pyridinyl]oxy]methyl]-2'-propyl [1,1'-biphenyl]-2-sulfonamide;
- N-(4,5-Dimethyl-3-isoxazolyl)-4'-[[3-ethoxy-6-ethyl-2-methyl-4-pyridinyl]oxy]methyl]-2'-ethyl [1,1'-biphenyl]-2-sulfonamide;
- 25 N-(3,4-Dimethyl-5-isoxazolyl)-4'-[[3-ethoxy-6-ethyl-2-methyl-4-pyridinyl]oxy]methyl]-2'-ethyl [1,1'-biphenyl]-2-sulfonamide;
- N-(4,5-Dimethyl-3-isoxazolyl)-4'-[[3-ethoxy-6-ethyl-2-methyl-4-pyridinyl]oxy]methyl]-2'-ethoxymethyl [1,1'-biphenyl]-2-sulfonamide;
- 30 N-(3,4-Dimethyl-5-isoxazolyl)-4'-[[3-ethoxy-6-ethyl-2-methyl-4-pyridinyl]oxy]methyl]-2'-ethoxymethyl [1,1'-biphenyl]-2-sulfonamide;

N-(4,5-Dimethyl-3-isoxazolyl)-4'-[[[(3-ethoxy-6-ethyl-2-methyl-4-pyridinyl)oxy]methyl]-2'-propyl [1,1'-biphenyl]-2-sulfonamide;

N-(3,4-Dimethyl-5-isoxazolyl)-4'-[[[(3-ethoxy-6-ethyl-2-methyl-4-pyridinyl)oxy]methyl]-2'-propyl [1,1'-biphenyl]-2-sulfonamide;

5 N-(4,5-Dimethyl-3-isoxazolyl)-4'-[[[(3-ethoxy-2-methyl-6-propyl-4-pyridinyl)oxy]methyl]-2'-ethyl [1,1'-biphenyl]-2-sulfonamide;

N-(3,4-Dimethyl-5-isoxazolyl)-4'-[[[(3-ethoxy-2-methyl-6-propyl-4-pyridinyl)oxy]methyl]-2'-ethyl [1,1'-biphenyl]-2-sulfonamide;

10 N-(4,5-Dimethyl-3-isoxazolyl)-4'-[[[(3-ethoxy-2-methyl-6-propyl-4-pyridinyl)oxy]methyl]-2'-ethoxymethyl [1,1'-biphenyl]-2-sulfonamide;

N-(3,4-Dimethyl-5-isoxazolyl)-4'-[[[(3-ethoxy-2-methyl-6-propyl-4-pyridinyl)oxy]methyl]-2'-ethoxymethyl [1,1'-biphenyl]-2-sulfonamide;

N-(4,5-Dimethyl-3-isoxazolyl)-4'-[[[(3-ethoxy-2-methyl-6-propyl-4-pyridinyl)oxy]methyl]-2'-propyl [1,1'-biphenyl]-2-sulfonamide;

15 N-(3,4-Dimethyl-5-isoxazolyl)-4'-[[[(3-ethoxy-2-methyl-6-propyl-4-pyridinyl)oxy]methyl]-2'-propyl [1,1'-biphenyl]-2-sulfonamide;

N-(4,5-Dimethyl-3-isoxazolyl)-4'-[[[(2,6-dimethyl-3-ethoxy-4-pyridinyl)oxy]methyl]-2'-ethyl [1,1'-biphenyl]-2-sulfonamide;

20 N-(3,4-Dimethyl-5-isoxazolyl)-4'-[[[(2,6-dimethyl-3-ethoxy-4-pyridinyl)oxy]methyl]-2'-ethyl [1,1'-biphenyl]-2-sulfonamide;

N-(4,5-Dimethyl-3-isoxazolyl)-4'-[[[(2,6-dimethyl-3-ethoxy-4-pyridinyl)oxy]methyl]-2'-ethoxymethyl [1,1'-biphenyl]-2-sulfonamide;

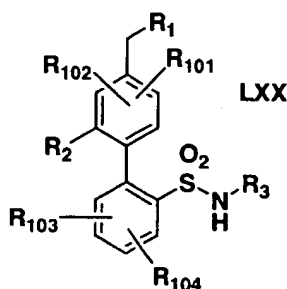
N-(3,4-Dimethyl-5-isoxazolyl)-4'-[[[(2,6-dimethyl-3-ethoxy-4-pyridinyl)oxy]methyl]-2'-ethoxymethyl [1,1'-biphenyl]-2-sulfonamide;

25 N-(4,5-Dimethyl-3-isoxazolyl)-4'-[[[(2,6-dimethyl-3-ethoxy-4-pyridinyl)oxy]methyl]-2'-propyl [1,1'-biphenyl]-2-sulfonamide;

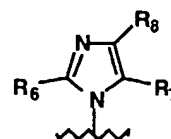
N-(3,4-Dimethyl-5-isoxazolyl)-4'-[[[(2,6-dimethyl-3-ethoxy-4-pyridinyl)oxy]methyl]-2'-propyl [1,1'-biphenyl]-2-sulfonamide;

and salts, enantiomers, diastereomers and metabolites thereof.

26. A compound of formula LXX, or an enantiomer, diastereomer, salt or metabolite thereof



- 5 wherein R_2 , R_{101} , R_{102} , R_{103} , R_{104} are as defined in claim 1;
 R_3 is isoxazol-5-yl or isoxazol-3-yl independently substituted with two
substituents selected from alkyl or halogen; and
 R_1 is any group such that the resulting compound demonstrates affinity
(IC₅₀) for both the AT₁ receptor and ET_A receptor of less than 5
10 micromolar at both receptors.



27. A compound of claim 2, wherein R_1 is M

28. A compound of claim 27, wherein R_2 is alkyl, haloalkyl,
alkoxyalkyl or haloalkoxyalkyl and R_{101} , R_{102} , R_{103} , R_{104} are each
15 independently hydrogen, halogen, or alkyl.

29. A compound of claim 27, wherein R_2 is $-\text{CH}_2\text{Y}$.

30. A compound of claim 29, wherein Y is Q.

20

31. A crystalline form of 4'-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-N-(4,5-dimethyl-3-isoxazolyl)-2'-(ethoxymethyl) [1,1'-biphenyl]-2-sulfonamide having a melting point of about 148°C.

32. A compound of claim 1 selected from
- 4'-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-3'-chloro-N-(4,5-dimethyl-3-isoxazolyl)-5-methoxy[1,1'-biphenyl]-2-sulfonamide;
- 5 4'-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-N-(4,5-dimethyl-3-isoxazolyl)-3'-fluoro-4-methoxy[1,1'-biphenyl]-2-sulfonamide;
- 4'-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-5'-chloro-N-(4,5-dimethyl-3-isoxazolyl)-2'-fluoro-4-methoxy[1,1'-biphenyl]-2-sulfonamide;
- 10 4'-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-3'-chloro-N-(4,5-dimethyl-3-isoxazolyl)-4-methoxy[1,1'-biphenyl]-2-sulfonamide;
- 4'-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-N-(4,5-dimethyl-3-isoxazolyl)-4-methoxy[1,1'-biphenyl]-2-sulfonamide;
- 4'-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-N-(4,5-dimethyl-3-isoxazolyl)-2'-(ethoxymethyl)-4-methoxy[1,1'-biphenyl]-2-sulfonamide;
- 15 4'-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-N-(4,5-dimethyl-3-isoxazolyl)-3'-fluoro-5-methoxy[1,1'-biphenyl]-2-sulfonamide;
- 4'-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-5'-chloro-N-(4,5-dimethyl-3-isoxazolyl)-2'-fluoro-5-methoxy[1,1'-biphenyl]-2-sulfonamide;
- 20 4'-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-N-(4,5-dimethyl-3-isoxazolyl)-5-methoxy[1,1'-biphenyl]-2-sulfonamide;
- 4'-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-N-(4,5-dimethyl-3-isoxazolyl)-2'-(ethoxymethyl)-5-methoxy[1,1'-biphenyl]-2-sulfonamide;
- 25 4'-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-N-(4,5-dimethyl-3-isoxazolyl)-3'-fluoro-4,5-dimethoxy[1,1'-biphenyl]-2-sulfonamide;

- 4'-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-5'-chloro-N-(4,5-dimethyl-3-isoxazolyl)-2'-fluoro-4,5-dimethoxy[1,1'-biphenyl]-2-sulfonamide;
- 5 4'-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-3'-chloro-N-(4,5-dimethyl-3-isoxazolyl)-4,5-dimethoxy[1,1'-biphenyl]-2-sulfonamide;
- 4'-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-N-(4,5-dimethyl-3-isoxazolyl)-4,5-dimethoxy[1,1'-biphenyl]-2-sulfonamide;
- 4'-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-N-(4,5-dimethyl-3-isoxazolyl)-2'-(ethoxymethyl)-4,5-dimethoxy[1,1'-biphenyl]-2-sulfonamide;
- 10 4'-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-5'-chloro-N-(4,5-dimethyl-3-isoxazolyl)-2'-fluoro[1,1'-biphenyl]-2-sulfonamide;
- 4'-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-3'-chloro-N-(4,5-dimethyl-3-isoxazolyl)[1,1'-biphenyl]-2-sulfonamide;
- 15 4'-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-N-(4,5-dimethyl-3-isoxazolyl)-4-methoxy-3'-methyl[1,1'-biphenyl]-2-sulfonamide;
- 4'-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-N-(4,5-dimethyl-3-isoxazolyl)-3'-fluoro-4-methoxy[1,1'-biphenyl]-2-sulfonamide;
- 4'-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-N-(4,5-dimethyl-3-isoxazolyl)-3'-methyl[1,1'-biphenyl]-2-sulfonamide;
- 20 4'-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-N-(4,5-dimethyl-3-isoxazolyl)-5-fluoro[1,1'-biphenyl]-2-sulfonamide;
- N²-(Cyclopropylcarbonyl)-N²-[[2'-[(4,5-dimethyl-3-isoxazolyl)amino]sulfonyl][1,1'-biphenyl]-4-yl)methyl]-N-methyl-L-
- 25 valinamide;
- N²-[[2'-[(4,5-Dimethyl-3-isoxazolyl)amino]sulfonyl][1,1'-biphenyl]-4-yl)methyl]-N,3-dimethyl-N²-(1-oxobutyl)-L-valinamide;
- N²-[[2'-[(4,5-Dimethyl-3-isoxazolyl)amino]sulfonyl][1,1'-biphenyl]-4-yl)methyl]-N-methyl-N²-(2-methyl-1-oxopropyl)-L-valinamide;

N²-(Cyclopentylcarbonyl)-N²-[[2'-[[[(4,5-dimethyl-3-isoxazolyl)amino]sulfonyl][1,1'-biphenyl]-4-yl]methyl]-N-methyl-L-valinamide;

5 N²-[[2'-[[[(4,5-Dimethyl-3-isoxazolyl)amino]sulfonyl]-3-fluoro[1,1'-biphenyl]-4-yl]methyl]-N-methyl-N²-(1-oxobutyl)-L-valinamide;

N²-[[2'-[[[(4,5-Dimethyl-3-isoxazolyl)amino]sulfonyl][1,1'-biphenyl]-4-yl]methyl]-N-(1-methylethyl)-N²-(1-oxobutyl)-L-valinamide;

N²-[[2'-[[[(4,5-Dimethyl-3-isoxazolyl)amino]sulfonyl][1,1'-biphenyl]-4-yl]methyl]-N-(2-methoxyethyl)-N²-(1-oxobutyl)-L-valinamide;

10 N-(Cyclopropylmethyl)-N²-[[2'-[[[(4,5-dimethyl-3-isoxazolyl)amino]sulfonyl][1,1'-biphenyl]-4-yl]methyl]-N²-(1-oxobutyl)-L-valinamide;

N²-[[2'-[[[(4,5-Dimethyl-3-isoxazolyl)amino]sulfonyl][1,1'-biphenyl]-4-yl]methyl]-N²-(1-oxobutyl)-N-(3-pyridinyl)-L-valinamide;

15 N²-[[2'-[[[(4,5-Dimethyl-3-isoxazolyl)amino]sulfonyl][1,1'-biphenyl]-4-yl]methyl]-N-methyl-N²-(1-oxopentyl)-L-valinamide;

N-Methyl-N²-[[2'-[[[(5-methyl-3-isoxazolyl)amino]sulfonyl][1,1'-biphenyl]-4-yl]methyl]-N²-(1-oxopentyl)-L-valinamide;

20 N²-[[2'-[[[(4,5-Dimethyl-3-isoxazolyl)amino]sulfonyl][1,1'-biphenyl]-4-yl]methyl]-N-ethyl-N²-(1-oxobutyl)-L-valinamide;

N²-[[2'-[[[(4,5-Dimethyl-3-isoxazolyl)amino]sulfonyl]-5'-fluoro[1,1'-biphenyl]-4-yl]methyl]-N-methyl-N²-(1-oxobutyl)-L-valinamide;

N-(4,5-Dimethyl-3-isoxazolyl)-4'-[[[(2,6-dimethyl-3-methoxy-4-pyridinyl)oxy]methyl][1,1'-biphenyl]-2-sulfonamide;

25 N-(4,5-Dimethyl-3-isoxazolyl)-4'-[[[(2,6-dimethyl-3-methoxy-4-pyridinyl)oxy]methyl]-3'-fluoro[1,1'-biphenyl]-2-sulfonamide;

N-(4,5-Dimethyl-3-isoxazolyl)-4'-[(1,4,5,6,7,8-hexahydro-8-oxo-2-propyl-1-cycloheptimidazolyl)methyl][1,1'-biphenyl]-2-sulfonamide;

30 N-(4,5-Dimethyl-3-isoxazolyl)-3'-fluoro-4'-[(1,4,5,6,7,8-hexahydro-8-oxo-2-propyl-1-cycloheptimidazolyl)methyl][1,1'-biphenyl]-2-sulfonamide;

N-(4,5-Dimethyl-3-isoxazolyl)-5-fluoro-4'-[(1,4,5,6,7,8-hexahydro-8-oxo-2-propyl-1-cycloheptimidazolyl)methyl][1,1'-biphenyl]-2-sulfonamide;

4'-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-N-(4,5-dimethyl-3-isoxazolyl)-2'-(hydroxymethyl)[1,1'-biphenyl]-2-sulfonamide;

5 N-[[2'-[(4,5-Dimethyl-3-isoxazolyl)amino]sulfonyl]-2-(ethoxymethyl)[1,1'-biphenyl]-4-yl)methyl]-1-[(1-oxopentyl)amino]cyclopentanamide;

and salts, enantiomers, diastereomers and metabolites thereof.

10 33. A compound of claim 1 selected from

4'-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-3'-chloro-N-(3,4-dimethyl-5-isoxazolyl)-5-methoxy[1,1'-biphenyl]-2-sulfonamide;

4'-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-N-(3,4-dimethyl-5-isoxazolyl)-3'-fluoro-4-methoxy[1,1'-biphenyl]-2-sulfonamide;

15 4'-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-5'-chloro-N-(3,4-dimethyl-5-isoxazolyl)-2'-fluoro-4-methoxy[1,1'-biphenyl]-2-sulfonamide;

4'-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-3'-chloro-N-(3,4-dimethyl-5-isoxazolyl)-4-methoxy[1,1'-biphenyl]-2-sulfonamide;

20 4'-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-N-(3,4-dimethyl-5-isoxazolyl)-4-methoxy[1,1'-biphenyl]-2-sulfonamide;

4'-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-N-(3,4-dimethyl-5-isoxazolyl)-2'-(ethoxymethyl)-4-methoxy[1,1'-biphenyl]-2-sulfonamide;

25 4'-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-N-(3,4-dimethyl-5-isoxazolyl)-3'-fluoro-5-methoxy[1,1'-biphenyl]-2-sulfonamide;

4'-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-5'-chloro-N-(3,4-dimethyl-5-isoxazolyl)-2'-fluoro-5-methoxy[1,1'-biphenyl]-2-sulfonamide;

30 4'-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-N-(3,4-dimethyl-5-isoxazolyl)-5-methoxy[1,1'-biphenyl]-2-sulfonamide;

4'-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-N-(3,4-dimethyl-5-isoxazolyl)-2'-(ethoxymethyl)-5-methoxy[1,1'-biphenyl]-2-sulfonamide;

4'-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-N-(3,4-dimethyl-5-isoxazolyl)-3'-fluoro-4,5-dimethoxy[1,1'-biphenyl]-2-sulfonamide;

4'-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-5'-chloro-N-(3,4-dimethyl-5-isoxazolyl)-2'-fluoro-4,5-dimethoxy[1,1'-biphenyl]-2-sulfonamide;

10 4'-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-3'-chloro-N-(3,4-dimethyl-5-isoxazolyl)-4,5-dimethoxy[1,1'-biphenyl]-2-sulfonamide;

4'-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-N-(3,4-dimethyl-5-isoxazolyl)-4,5-dimethoxy[1,1'-biphenyl]-2-sulfonamide;

4'-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-N-(3,4-dimethyl-5-isoxazolyl)-2'-(ethoxymethyl)-4,5-dimethoxy[1,1'-biphenyl]-2-sulfonamide;

4'-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-5'-chloro-N-(3,4-dimethyl-5-isoxazolyl)-2'-fluoro[1,1'-biphenyl]-2-sulfonamide;

4'-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-3'-chloro-N-(3,4-dimethyl-5-isoxazolyl)[1,1'-biphenyl]-2-sulfonamide;

4'-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-N-(3,4-dimethyl-5-isoxazolyl)-4-methoxy-3'-methyl[1,1'-biphenyl]-2-sulfonamide;

4'-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-N-(3,4-dimethyl-5-isoxazolyl)-3'-fluoro-4-methoxy[1,1'-biphenyl]-2-sulfonamide;

25 4'-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-N-(3,4-dimethyl-5-isoxazolyl)-3'-methyl[1,1'-biphenyl]-2-sulfonamide;

4'-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-N-(3,4-dimethyl-5-isoxazolyl)-5-fluoro[1,1'-biphenyl]-2-sulfonamide;

N²-(Cyclopropylcarbonyl)-N²-[[2'-[(3,4-dimethyl-5-isoxazolyl)amino]sulfonyl][1,1'-biphenyl]-4-yl)methyl]-N-methyl-L-valinamide;

- N²-[[2'-[[[(3,4-Dimethyl-5-isoxazolyl)amino]sulfonyl][1,1'-biphenyl]-4-yl]methyl]-N,3-dimethyl-N²-(1-oxobutyl)-L-valinamide;
- N²-[[2'-[[[(3,4-Dimethyl-5-isoxazolyl)amino]sulfonyl][1,1'-biphenyl]-4-yl]methyl]-N-methyl-N²-(2-methyl-1-oxopropyl)-L-valinamide;
- 5 N²-(Cyclopentylcarbonyl)-N²-[[2'-[[[(3,4-dimethyl-5-isoxazolyl)amino]sulfonyl][1,1'-biphenyl]-4-yl]methyl]-N-methyl-L-valinamide;
- N²-[[2'-[[[(3,4-dimethyl-5-isoxazolyl)amino]sulfonyl]-3-fluoro[1,1'-biphenyl]-4-yl]methyl]-N-methyl-N²-(1-oxobutyl)-L-valinamide;
- 10 N²-[[2'-[[[(3,4-dimethyl-5-isoxazolyl)amino]sulfonyl][1,1'-biphenyl]-4-yl]methyl]-N-(1-methylethyl)-N²-(1-oxobutyl)-L-valinamide;
- N²-[[2'-[[[(3,4-dimethyl-5-isoxazolyl)amino]sulfonyl][1,1'-biphenyl]-4-yl]methyl]-N-(2-methoxyethyl)-N²-(1-oxobutyl)-L-valinamide;
- N-(Cyclopropylmethyl)-N²-[[2'-[[[(3,4-dimethyl-5-isoxazolyl)amino]sulfonyl][1,1'-biphenyl]-4-yl]methyl]-N²-(1-oxobutyl)-L-valinamide;
- 15 N²-[[2'-[[[(3,4-Dimethyl-5-isoxazolyl)amino]sulfonyl][1,1'-biphenyl]-4-yl]methyl]-N²-(1-oxobutyl)-N-(3-pyridinyl)-L-valinamide;
- N²-[[2'-[[[(3,4-Dimethyl-5-isoxazolyl)amino]sulfonyl][1,1'-biphenyl]-4-yl]methyl]-N-methyl-N²-(1-oxopentyl)-L-valinamide;
- 20 N-Methyl-N²-[[2'-[[[(3-methyl-5-isoxazolyl)amino]sulfonyl][1,1'-biphenyl]-4-yl]methyl]-N²-(1-oxopentyl)-L-valinamide;
- N²-[[2'-[[[(3,4-Dimethyl-5-isoxazolyl)amino]sulfonyl][1,1'-biphenyl]-4-yl]methyl]-N-ethyl-N²-(1-oxobutyl)-L-valinamide;
- 25 N²-[[2'-[[[(3,4-Dimethyl-5-isoxazolyl)amino]sulfonyl]-5'-fluoro[1,1'-biphenyl]-4-yl]methyl]-N-methyl-N²-(1-oxobutyl)-L-valinamide;
- N-(3,4-Dimethyl-5-isoxazolyl)-4'-[[[(2,6-dimethyl-3-methoxy-4-pyridinyl)oxy]methyl][1,1'-biphenyl]-2-sulfonamide;
- N-(3,4-Dimethyl-5-isoxazolyl)-4'-[[[(2,6-dimethyl-3-methoxy-4-pyridinyl)oxy]methyl]-3'-fluoro[1,1'-biphenyl]-2-sulfonamide;
- 30

N-(3,4-Dimethyl-5-isoxazolyl)-4'-[(1,4,5,6,7,8-hexahydro-8-oxo-2-propyl-1-cycloheptimidazolyl)methyl][1,1'-biphenyl]-2-sulfonamide;

N-(3,4-Dimethyl-5-isoxazolyl)-3'-fluoro-4'-[(1,4,5,6,7,8-hexahydro-8-oxo-2-propyl-1-cycloheptimidazolyl)methyl][1,1'-biphenyl]-2-sulfonamide;

5 N-(3,4-Dimethyl-5-isoxazolyl)-5-fluoro-4'-[(1,4,5,6,7,8-hexahydro-8-oxo-2-propyl-1-cycloheptimidazolyl)methyl][1,1'-biphenyl]-2-sulfonamide;

4'-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-N-(3,4-dimethyl-5-isoxazolyl)-2'-(hydroxymethyl)[1,1'-biphenyl]-2-sulfonamide;

10 N-[[2'-[(3,4-Dimethyl-5-isoxazolyl)amino]sulfonyl]-2-(ethoxymethyl)[1,1'-biphenyl]-4-yl)methyl]-1-[(1-oxopentyl)amino]cyclopentanamide;

and salts, enantiomers, diastereomers and metabolites thereof.

34. The compound 4'-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-N-(4,5-dimethyl-3-isoxazolyl)-2'-(2-fluoroethoxymethyl) [1,1'-biphenyl]-2-sulfonamide or a salt, enantiomer, diastereomer or metabolite thereof.

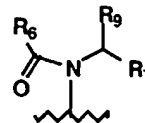
35. The compound 4'-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-N-(4,5-dimethyl-3-isoxazolyl)-2'-propyl [1,1'-biphenyl]-2-sulfonamide or a salt, enantiomer, diastereomer or metabolite thereof.

36. The compound N-(4,5-Dimethyl-3-isoxazolyl)-2'-ethoxymethyl-4'-[[[(3-methoxy-2,6-dimethyl-4-pyridinyl)oxy]methyl] [1,1'-biphenyl]-2-sulfonamide or a salt, enantiomer, diastereomer or metabolite thereof.

37. The compound N-(4,5-Dimethyl-3-isoxazolyl)-2'-[(2-fluoroethoxy)methyl]-4'-[[[(3-methoxy-2,6-dimethyl-4-pyridinyl)oxy]methyl] [1,1'-biphenyl]-2-sulfonamide or a salt, enantiomer, diastereomer or metabolite thereof.

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38. The compound N-(4,5-Dimethyl-3-isoxazolyl)-4'-[[[(3-methoxy-2,6-dimethyl-4-pyridinyl)oxy]methyl]-2'-propyl [1,1'-biphenyl]-2-sulfonamide or a salt, enantiomer, diastereomer or metabolite thereof.



5 39. A compound of claim 2, where in R_1 is D.

40. A compound of claim 39, wherein R_2 is hydrogen, alkyl, haloalkyl, alkoxyalkyl or haloalkoxyalkyl and R_{101} , R_{102} , R_{103} , R_{104} are each independently hydrogen, halogen, or alkyl.

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41. A compound of claim 39 wherein R_2 is $-CH_2Y$.

42. A compound of claim 41, wherein Y is Q.

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43. A compound of claim 1 wherein R_3 is other than pyridyl when R_1 is A.

44. The pharmaceutical composition of claim 46 further comprising at least one ACE inhibitor (such as captopril, zofenopril, fosinopril, ceranapril, alacepril, enalapril, delapril, pentopril, quinapril, ramipril, or lisinopril), vasopepsidase inhibitor (such as omapatrilat or gemopatrilat), HMG CoA reductase inhibitor (such as pravastatin, lovastatin, atorvastatin, simvastatin, NK-104 or ZD-4522), anti-platelet agent (such as clopidigrel, ticlopidine, CS-747 or aspirin), anti-diabetic agent (such as biguanides or biguanide/glyburide combinations), beta-adrenergic agent (such as

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carvedilol or metoprolol), or mineralocorticoid receptor antagonist (such as spironolactone or eplerenone).

45. The compound (+)-4'-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-N-(4,5-dimethyl-3-isoxazolyl)-2'-(ethoxymethyl) [1,1'-biphenyl]-2-sulfonamide or metabolites and salts thereof.

46. The compound (-)-4'-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-N-(4,5-dimethyl-3-isoxazolyl)-2'-(ethoxymethyl) [1,1'-biphenyl]-2-sulfonamide or metabolites and salts thereof.